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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/774,681	02/01/2001	Linda A. Sherman	313332000101	3045

21874 7590 08/27/2002

DIKE, BRONSTEIN, ROBERTS AND CUSHMAN,
INTELLECTUAL PROPERTY PRACTICE GROUP
EDWARDS & ANGELL, LLP.
P.O. BOX 9169
BOSTON, MA 02209

EXAMINER	
DECLOUX, AMY M	
ART UNIT	**PAPER NUMBER**
1644	13

DATE MAILED: 08/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Incomplete
Obj to spec pg 2

Office Action Summary	Application N .	Applicant(s)	
	09/774,681	SHERMAN ET AL.	
	Examiner	Art Unit	
	Amy M. DeCloux	1644	

-- The MAILING DATE of this c mmunication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-21* is/are pending in the application.

4a) Of the above claim(s) *20 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The Examiner and Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Amy DeCloux, Group Art Unit 1644, Group 1640, Technology Center 1600.

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 6-19, in Paper No. 12, Filed 6-3-02, is acknowledged. The traversal is on the ground(s) that adding claims 20 and/or 21 to the elected group would not pose an undue burden on the USPTO, and that the search for Groups II and/or III would significantly overlap with a search for Group I. This is not found persuasive because though the searches for Group I and Group II and/or III might overlap, the searches for each respective group are not coextensive, and therefore an undue search burden would be imposed on the examiner.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 19-20 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 12, filed 6-3-02.

3. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Specification

The disclosure is objected to because of the following informalities: Page 12 of the specification contains two blank spaces that are underlined on line 17.

Appropriate correction is required.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

5. Claims 6-8, 10-11 and 13-18 are rejected under 35 U.S.C. 102(a) as being anticipated by Mule (WO 05/06409).

Mule teaches a DNA molecule encoding a chimeric TCR that encodes a protein comprising a the TCR α and/or β-ζ of the TCR that recognizes peptides found on the surface of a particular cancer cell type, under the transcriptional control of the LTR from Moloney Murine Leukemia virus that can be used for the recognition and destruction of cancer cells, (see entire patent, especially page 15, lines 5-27, and lines 31-35, and Example 6). Mule also teaches that said construct encoding a cancer cell specific for a recombinant polypeptide can be transduced into a T cell line, and the transduced into a T cell line and assayed for its ability to lyse cancer cells expressing the protein recognized by the recombinant polypeptide (see entire patent, especially page 17, lines 13-22). Mule also teaches transfection of said construct into hematopoietic stem cells from a human host and subsequent repopulation of said transfected cells into the human host for differentiation into T cells (see entire patent, especially page 18). Thus, no matter what non-human species the Variable region of the TCR is derived from, the TCR will be human HLA-restricted. Therefore, the referenced teachings anticipate the claimed invention.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 6-9 and 15-17 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Engel et al (1992) Science 256:1318-1321, in view of Mule (WO 95/06409).

Engel et al teaches an isolated nucleic acid molecule which comprises a nucleotide sequence encoding a variable region of a non-human TCR isolated from the T cell hybridoma

2B4 fused to the transmembrane and cytoplasmic domains of murine TCR ζ (see entire article, including page 1318, column 2, last paragraph, page 1320, column 2, last paragraph, and page 1319, legend of Figure 1(A)). Engel et al teach that the T cell hybridoma 2B4 recognizes a peptide derived from cytochrome C bound to the murine MHC encoded molecule I-E^k . Engel teaches that said nucleic acid molecule was transfected and expressed in the rat basophilic leukemia line RBL-2H3.

Engel et al also teach that the attachment of the ζ chain transmembrane and cytoplasmic domains to the TCR α and β chain extracellular domains provides for the efficient production and cell surface expression of αβ heterodimers , and that this approach has also been used with two human αβ heterodimers, as well as the above mentioned murine αβ heterodimers and appears to be a generalizable approach (see entire article, including the last full paragraph on page 1320). Engel et al also teach that this approach could be used to generate antibodies to TCRs that recognize native epitopes, (see entire article, including column 3 of page 1320).

Engel et al does not specifically teach that the TCR is specific for a tumor associated antigen.

Mule teaches as above.

Therefore, one of skill would have been motivated to substitute a nucleic acid molecule encoding the tumor specific antigen binding site of the chimeric TCR molecule taught by Mule for the cytochrome C antigen binding site of the chimeric molecule taught by Engel et al. because Engel teaches that the approach of making an isolated nucleic acid molecule which comprises a nucleotide sequence encoding a variable region of a TCR fused to the transmembrne and cytoplasmic domains of murine TCR ζ is a generalizable approach and Mule teaches that a chimeric TCR encoded by said nucleic acid could be used for the recognition and/or destruction of cancer cells.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

7. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mule (WO 95/06409), in view of Reinherz et al (US Patent No. 6,416,971, 7-9-02, filed 5-8-1991).

Mule teaches as above.

Mule does not teach a nucleic acid molecule comprising the flexible linker of SEQ ID NO:65.

'971 teaches a nucleic acid molecule encoding a single chain T cell receptor and that the identity of the amino acids in the amino acid linker used to join the Ti subunit fragments is not critical. It is only necessary that the linker be capable of permitting the joined Ti subunit

fragments to associate in such a manner so as to form the antigen binding site. However, amino acids which impart flexibility and aqueous solubility are most desirable. Among amino acids which impart flexibility, glycine, stands apart as the most effective due to its lack of .beta.-carbons. Similarly, the length of the linker should be such as to allow the joined Ti subunit fragments to associate in such a manner so as to form the antigen binding site. The amino acid linker typically ranges from about 10 to about 30 amino acids in length, and is preferably about 15 to about 25 amino acids in length. A particularly preferred amino acid linker is one with the following sequence: Pro-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly -Gly-Ser-Gly-Ala. (see entire patent, especially column 4, lines 29-49).

Therefore one of skill who wanted to make a DNA molecule encoding a chimeric TCR that encodes a protein comprising a the TCR α and/or β-ζ of the TCR that recognizes peptides found on the surface of a particular cancer cell type as taught by Mule, would have been motivated to substitute a linker with the properties taught by '971 in place of the linker taught by Mule, since '971 teaches that the identity of the amino acids in the amino acid linker used to join the Ti subunit fragments in a single chain T cell receptor is not critical. '971 teaches that for a linker, amino acids which impart flexibility, such as glycine, should be used due to its lack of .beta.-carbons. '971 also teaches that the length of the linker should be such as to allow the joined Ti subunit fragments to associate in such a manner so as to form the antigen binding site. Since the length and amino acid composition of the linker recited in the instant claim is taught by '971, one of ordinary skill would have had an expectation of success in making and using a nucleic acid molecule comprising a region encoding a linker with the properties of '971 (such as SEQ ID NO:65) between the alpha and beta variable regions of a nucleic acid molecule encoding a recombinant single chain molecule.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 7-9 and 13-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 7-8 and 13-14 are indefinite in the recitation of "the ζ region of CD3, CD8 or CD16",(claim 7), "said ζ region is that of human CD3, CD8 or CD16",(claims 8 and 13), and "the ζ chain is derived from human CD3, CD8 or CD16" (claim 14), because it

is not clear exactly what the different ζ chains are. Clarification is required, perhaps in the form of SEQ ID NO:s.

B) Claim 9 is indefinite in its recitation of "The nucleic acid molecule wherein said non-human TCR is murine." There is insufficient antecedent basis for the limitation of "said non-human TCR" in the claim.

Conclusion

No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy M. DeCloux whose telephone number is 703 306-5821. The examiner can normally be reached on M-F 8:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 703 308-3973. The fax phone numbers for the organization where this application or proceeding is assigned are 703 305-3014 for regular communications and 703 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308-0196.

Amy DeCloux, PhD,
Patent Examiner,
August 25, 2002

Patrick J. Nolan, Ph.D.,
Primary Patent Examiner,